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Neonatal meningococcal disease in the United States, 1990 to 1999

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Background. **Although neonatal bacterial meningitis is common, the rate of invasive meningococcal disease in the United States among children ≤30 days old has not been defined. Most relevant literature consists of case reports or case series, which note high case-fatality ratios but do not describe the overall burden of disease.**

Methods. **We used active, population-based surveillance data from the Active Bacterial Core Surveillance program to estimate the incidence of neonatal meningococcal disease in the United States from 1990 to 1999. A case of neonatal meningococcal disease was defined as isolation of *Neisseria meningitidis* from a normally sterile site in a resident of the surveillance area ≤30 days of age.**

Results. **The median annual number of neonates under surveillance was 25 900. Between 1990 and 1999, 22 cases of neonatal meningococcal disease were identified. Three (14%) patients died. The average annual incidence was 9 per 100 000.**

Conclusions. **The rate of neonatal meningococcal disease in the United States is higher than previous estimates. Meningococcal disease is un-**

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common in neonates, but its rate is similar to that of meningococcal disease in 6- to 23-month-old children.

INTRODUCTION

Neisseria meningitidis is a leading cause of bacterial meningitis and septicemia in children and adolescents in the United States, with attack rates highest among children younger than 2 years of age.[1] Despite the high incidence of bacterial meningitis in neonates, the rate of invasive meningococcal disease among children ≤30 days old has not been well-defined. To date most of the relevant literature consists of case reports or case series, which are notable for their high case-fatality ratios but provide no information as to the overall burden of disease.[2–8] Incidence estimates for neonatal meningococcal disease in other countries have been published,[9] but determining a rate for the United States based on those data is not possible given the variable distribution of meningococcal disease worldwide. Previous estimates of the incidence of neonatal meningococcal disease in the United States have been based on passive surveillance or on active surveillance in a small area or for a short period of time.[10–12]

We used data from active, population-based surveillance in large and diverse portions of the United States from 1990 through 1999 to estimate the incidence of neonatal meningococcal disease and project the number of cases that occurred in neonates in the United States each year.

METHODS

During 1990 through 1999, we conducted active laboratory-based surveillance using methods previously described as part of the Active Bacterial Core Surveillance (ABCs) program.[10] The sites under surveillance varied each year but included statewide data from Connecticut, Georgia, Maryland, Oklahoma, Missouri, Minnesota and Oregon and multicounty area data from California, New York and Tennessee. The aggregate population under surveillance ranged from ~10 million in 1991 to >31 million in 1999.

A case of neonatal meningococcal disease was defined as isolation of *N. meningitidis* from a normally sterile site [e.g. blood, cerebrospinal fluid (CSF) or synovial fluid] in a resident of the surveillance area who was ≤30 days of age when the culture was obtained. Cases were considered early onset if the patient was ≤7days of age when the culture was obtained and late onset if the patient was 8 to 30 days of age. A case of meningococcal meningitis was defined as growth of *N. meningitidis* in a CSF culture. Surveillance officers communicated regularly with all microbiology laboratories in each surveillance area and completed standardized case report forms. Periodic audits by review of microbiology records at reporting laboratories have demonstrated a sensitivity of 96 to 98% during the 1990s.[1] Cases newly identified by audit were included in the surveillance data.

Neonatal population denominators were calculated by obtaining US census estimates for the number of children <1 year of age in the appropriate area for each year studied and dividing by 12. The median annual number of neonates under surveillance was 25 900 (minimum 13 500 in 1990, maximum 36 400 in 1999). Black neonates represented 22% of the surveillance population, as compared with 15% of the US neonatal population. The rate of neonatal meningococcal disease was determined by dividing the total number of neonates with disease by the sum of all neonates in all surveillance areas from 1990 through 1999. Because ABCs oversamples blacks, rates were calculated separately for blacks and nonblacks before projecting the number of cases of culture-confirmed neonatal meningococcal disease in the US during this time.

The rates of neonatal meningitis and sepsis caused by *Haemophilus influenzae*, *Streptococcus pneumoniae* and group B *Streptococcus* were determined using ABCs data for the years 1996 through 1999, with the use of similar case definitions (i.e. sterile site isolation). Counties and states under surveillance varied by year and organism. Incidence rates were calculated using the maximum US population under ABCs surveillance for each organism for each year. Incidence rates (cases per 100 000 persons) for each were calculated by dividing the total number of cases by the sum of all neonates in the surveillance area from 1996 through 1999.

Incidences of meningococcal disease during each month of life after the neonatal period and before 2 years of age for the years 1990 through 1999 were determined in a manner similar to that for neonatal rates. Incidences in children 6 to 11 and 12 to 23 months of age for 1990 through 1999 were determined by dividing the sum of monthly numerators by the combined denominator.

Statistical analysis was performed with Epi-Info (Version 6.02) software. The chi square or Fisher exact tests were used to compare proportions.

RESULTS

Between 1990 and 1999, 22 cases of neonatal meningococcal disease were identified in the surveillance area. Three (14%) patients died. Nine (41%) patients were male. Four (18%) were black, 17 (77%) were white and 4 (18%) were reported as Hispanic. The median age was 14 days (range, 0 to 29 days) (Fig. 1). Gestational age was available for 10 (45%) patients; the median gestational age for this group was 40 weeks (range, 36 to 41 weeks). In 16 (73%) of the 22 patients *N. meningitidis* was isolated from the CSF, including 6 patients who had growth in both CSF and blood cultures. The remaining 6 patients had growth in blood cultures

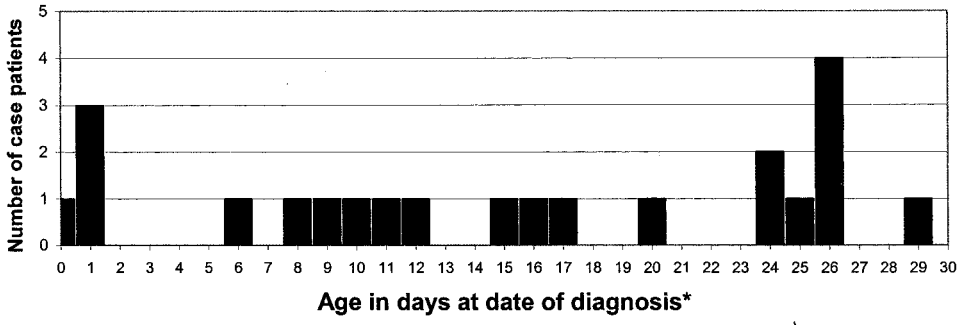

FIG. 1. Age (in days) of neonates with culture-confirmed meningococcal disease in selected areas of the United States.

only. Seasonal variation occurred with the highest proportion of cases reported during the months of December, January and February (n = 9; 41%). Of the 18 isolates for whom serogroup was known, 10 (55%) were serogroup B, 4 (22%) were serogroup C, 3 (17%) were serogroup Y and 1 (6%) was nongroupable.

Six (27%) patients were categorized as having early onset disease. The early and late onset groups did not differ significantly by race, sex, mortality or the presence of meningitis. Serogroup C was more likely to be recovered from the early onset group than from late onset patients (50% *vs.* 6%; P = 0.05).

At least one case of neonatal meningococcal disease was found at each site during its time under surveillance. From all sites a median of 2.5 cases occurred each year, ranging from no cases in 1994 to 5 cases in 1999. The average annual incidence of meningococcal disease for the areas under surveillance was 9.0 cases per 100 000 children ≤30 days old and ranged from 0 in 1994 to 22 per 100 000 in 1991. Rates did not vary significantly by race. On the basis of these data and after adjusting for race, we estimate that 29 cases of culture-confirmed meningococcal disease occurred annually among neonates in the United States from 1990 through 1999. Rates of meningococcal disease by age in months for children <2 years of age show a peak in incidence between 1 and 6 months of age (Fig. 2). The neonatal rate is similar to the rates among children 6 to 11 months of age (9/100 000) and 12 to 23 months of age (5 per 100 000). From 1996 through 1999 neonatal meningococcal disease was less common than neonatal disease caused by *H. influenzae* and *S. pneumoniae* and much less common than group B streptococcal disease (Table 1).

DISCUSSION

An accurate determination of the incidence of neonatal meningococcal disease in the United States has not been previously possible because neonatal meningococcal disease is uncommon and requires surveillance in a large, diverse population over a sufficient time to detect cases. This study indicates that the true rate of neonatal meningococcal disease in the United States is higher than previously measured rates, which were based on passive surveillance or active surveillance over a short period of time.[10, 11] *N. meningitidis* is not a major cause of neonatal meningitis and sepsis, but the rate of neonatal meningococcal infection is similar to that of meningococcal disease in 6- to 23-month-old children.

The similarity in the rates of meningococcal disease for neonates and older infants is surprising because of expected differences in the proportion of each group with protective antibodies. Serologic studies of US

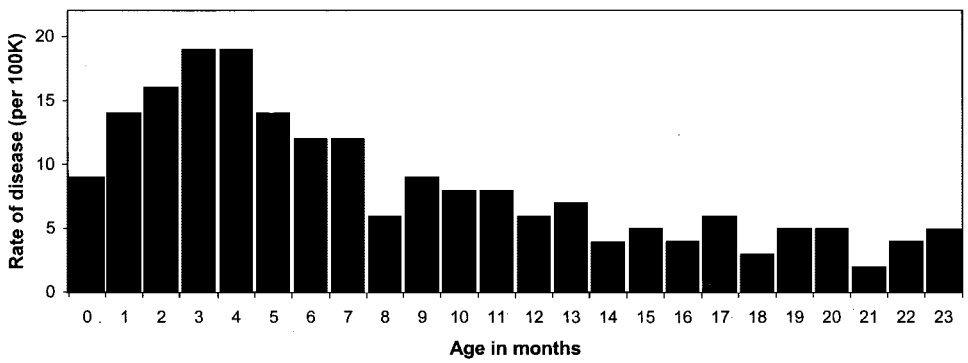

FIG. 2. Incidence (cases per 100 000 persons) of culture-confirmed meningococcal disease among children <2 years old in selected areas of the United States, 1990 to 1999.

TABLE 1. Incidence (cases per 100 000 persons) of culture-confirmed neonatal meningitis and sepsis in selected areas of the United States, by organism, 1996 to 1999

Causative Organism	No. of Cases Reported	Incidence
Neisseria meningitidis	12	9.0
Haemophilus influenzae	49	41.2
Streptococcus pneumoniae	36	45.2
Group B streptococci	1015	973.8

infants in the 1960s found that >50% of newborns have bactericidal antibodies against the major *N. meningitidis* serogroups causing disease in the US at that time.[13] These protective antibodies are received through passive transfer *in utero*, but gradually decline during the first 3 to 6 months of life; bactericidal antibodies are present in fewer than 25% of infants ages 6 to 23 months.[13] Prematurity decreases the likelihood of transfer of protective antibodies. However, among the patients in this study for whom gestational age was available, none was premature and most should have had protective antibodies.

Another critical element of immune defense against *N. meningitidis* is the complement-mediated phagocytosis of bacteria by neutrophils. Compared with older infants neonates have lower levels of terminal complement components, decreased numbers of neutrophils and a decreased capacity for neutrophils to adhere to endothelium and migrate to sites of infections.[14–16] These deficiencies may explain the susceptibility of some neonates to meningococcal infection despite the presence of maternally derived protective antibodies.

The primary objective of our study was to report incidence, but two other notable findings emerged. The neonatal case-fatality ratio was high (14%) but consistent with that of meningococcal disease among children 1 to 23 months of age (5%; CDC, unpublished data). It was much lower, however, than case-fatality ratios for neonatal meningococcal disease based on case reports (40 to 60%), which likely reflects reporting bias toward severe cases. Second, the proportion of neonates with meningococcal disease whose CSF yielded *N. meningitidis* isolates was higher (73%) than that among children 1 to 23 months of age with meningococcal disease (41%; CDC, unpublished data) and neonates with invasive group B streptococcal disease (6% early onset; 24% late onset).[17]

Theories concerning the manner of transmission of neonatal meningococcal disease have pointed to intrapartum transmission via the maternal genitourinary tract,[18, 19] acquisition *in utero*[20] and postpartum transmission in a manner similar to that of older patients. The similar incidence of early onset and late onset disease does not help to discern the more likely potential mode of transmission among those suggested. Although meningococcal vaccines with improved immunogenicity in infants and young children are currently under development, neonatal meningococcal disease, as well as neonatal *H. influenzae* and *S. pneumoniae* disease, will not be directly preventable by routine infant immunization. Alternative strategies such as maternal immunization or vaccination at birth are considerations.

APPENDIX

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Reduction in perinatal transmission and mortality from human immunodeficiency virus after intervention with zidovudine in Barbados

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Objectives. **To evaluate the impact of zidovudine (ZDV) intervention on vertical transmission and HIV-related mortality in two groups of pregnant mothers and their respective infants.**

Methods. **A modified long course Paediatric AIDS Clinical Trial Group 076 protocol was used. None of the infants was breast-fed. Maternal CD4 T lymphocyte counts and viral loads were not monitored. Infants were followed for clinical progress, and serial serologic testing was performed to the age of 24 months, or until two successive HIV (enzyme-linked immunosorbent assay) tests were negative. In a historically case-controlled prospective study, the transmission rate in ZDV-untreated mother-infant pairs in which infants were born during 1991 through 1995 was compared with the transmission rate in ZDV-treated mother-infant pairs in which infants were born between 1996 and 2000.**

Results. **In the 151 HIV-seropositive pregnant women and their 153 infants studied (2 pairs of twins), 93 mother-infant pairs were treated, and 59 were untreated (control group). Vertical transmission occurred in 5.5% [95% confidence interval (95% CI) 1.9 to 12.5] of the treated group of infants and in 27.1% (95% CI 16.7 to 40.5) of the untreated group. There was a 79.7% (95% CI 59.8 to 92.1%) relative reduction risk of transmission, which was statistically significant (z =3.18, two tailed P= 0.0001). Three infant deaths (3.7%) were recorded in the untreated group, and 1(1%) death was recorded in the treated group. In ZDV-untreated infants, deaths occurred at age <1 year, resulting from respiratory complications. One ZDV-treated infant died at 4 years of age with *Pneumocystis carinii* pneumonia.**

Conclusions. **Our study demonstrated a statistically significant reduction in the vertical transmission of HIV after intervention with ZDV therapy.**

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INTRODUCTION

Mother to child transmission of HIV ranges between 15 and 40%.[1–25] The perinatal route of spread remains